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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/508,516	06/08/2000	CHRISTOPHER ROBERT BEBBINGTON	078883/0119	3014

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	37

DATE MAILED: 09/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/508,516	BEBBINGTON ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,9-11,14-17,21,22,24,47,49-51,53-55 and 57-79* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,9-11,14-17,21,22,24,47,49-51,53-55 and 57-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *36* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-14-03 has been entered.

Applicant's arguments filed 6-14-03, paper number 35, have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Claims 1-3, 7, 8, 12-13, 18-20, 23, 25-46, 48, 52 and 56 have been canceled. Claims 60-79 have been entered. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-79 are pending and under consideration in the instant office action.

Claim R j ctions - 35 USC § 112

I. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-59 remain rejected and claims 60-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The phrases " whereby the first NOI is removed as a result of splicing" in claim 1 and "whereby an intervening sequence between the functional splice donor site and the functional splice acceptor site is removed as a result of splicing" in claim 57 are new matter. Applicants point to pg 30, lines 31-32, which states "[i]n another preferred aspect of the invention, the vector components are regulated by tetracycline on/off system."

II. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-59 remain rejected and claims 60-79 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for the selective expression of the hygromycin - neomycin gene pair or the hygromycin-p450 gene pair does not reasonably provide enablement for any nucleotide sequence of interest (NOI) as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record.

A brief summary of the examiner's view of the invention follows:

A retroviral pro-vector that produces retroviral particles used to transfer at least one nucleic acid to a target cell. The pro-vector has a 5' and 3' LTR, an engineered splice donor in the 3' LTR, a splice acceptor, a packaging signal and selectable gene, and an NOI (Fig. 27c). The pro-vector is transfected into packaging cells. The selectable marker is used to select packaging cells that have been successfully transfected. The packaging signal signals the production of viral particles comprising the pro-virus in the packaging cells. Viral particles comprising the pro-virus are used to infect target cells. Upon transcription of the pro-virus in target cells, translocation of the splice donor in the 3' LTR to the 5' LTR occurs. The presence of the splice donor upstream of the selectable marker/packaging signal and splice acceptor (in the 5' LTR) allows for splicing out the selectable marker/packaging signal. The virus integrated into the genome of the target cell is spliced and is shown in Fig. 27c. The virus integrated into the genome of the target cell has a 3' LTR with a splice donor, a portion of the 5' LTR and the second NOI. The virus integrated into the genome of the target cell does not have the entire 5' LTR or the first NOI (selectable marker/packaging signal) as claimed (1, 57). The virus integrated into the genome of the target cell has a splice donor fused with a splice acceptor and not a splice donor and acceptor as claimed (1, 57).

Claims 1 and 57 require a 5' LTR with a functional splice donor and a spliced NOI. Thus, the claim appears to be directed toward the virus once it has been transcribed and integrated into the host cell. First, the viruses of claims 1 and 57 are never in a retroviral particle as in claims 24 and 58 because they are only found in the

genome of the host cell; the integrated virus does not have packaging signals and cannot produce viral particles. Second, the locations of the elements in the pro-vector are essential to obtain the virus claimed, specifically to allow for selection of packaging cells transfected with the vector, packaging of the pro-vector into viral particles and splicing upon infecting target cells with the viral particles. Upon transfecting packaging cells with the pro-vector, the selectable marker is essential to select packaging cells successfully transfected. The packaging signal is essential to package the pro-virus into viral particles. The pro-virus must have a splice donor in the 3' LTR to end up in the 5' LTR of the virus once it is in target cells (upstream of the selectable marker, packaging signal and splice acceptor site) to allow for splicing of the selectable marker/packaging signal upon infection into target cells. The splice acceptor must be between the selectable marker/packaging signal and the NOI to splice out the selectable marker/packaging signal. Claims 1 and 57 are inaccurate because the virus integrated into the genome of the host cells does not have the first NOI as claimed. Nor does it have an entire splice donor in the 5' LTR or a splice acceptor as claimed. In addition, the virus must have a splice donor in the 3' LTR for translocation of the splice donor into the 5' LTR to occur. Thus, the virus claimed is not adequately described in the specification and would not allow translocation or splicing.

Claims 47 and 74 require a using a pro-vector having a 3' LTR with a functional splice donor and an NOI upstream of the splice acceptor and downstream of the 5' LTR to make a retroviral vector having a splice donor in the 5' LTR. Thus, the claims appear to be directed toward producing the spliced vector once it is integrated into a host cell

using the pro-virus. The locations of the elements in the pro-vector are essential to obtain the virus claimed, specifically to allow for selection of packaging cells transfected with the vector, packaging of the pro-vector into viral particles and splicing upon infecting target cells with the viral particles. Upon transfecting packaging cells with the pro-vector, the selectable marker is essential to select packaging cells successfully transfected. The packaging signal is essential to package the pro-virus into viral particles. The pro-virus must have a splice donor in the 3' LTR to end up in the 5' LTR of the virus once it is in target cells (upstream of the selectable marker, packaging signal and splice acceptor site) to allow for splicing of the selectable marker/packaging signal upon infection into target cells. The splice acceptor must be between the selectable marker/packaging signal and the NOI to splice out the selectable marker/packaging signal. Claims 47 and 74 are inaccurate because the pro-vector does not have the selectable marker and packaging signal, which are essential to obtain the vector with a splice donor in the 5' LTR as claimed. In addition, the phrase "packaging the retroviral pro-vector in a packaging cell, thereby producing a viral particle" lacks essential elements required to obtain the virus claimed because it does not accurately reflect the fact that packaging cells are transfected with the pro-vector or that viral particles comprising the pro-virus are produced in the packaging cells (see 112/2nd). In addition, the phrase "infecting a target cell... ...thereby producing a retroviral vector comprising a functional splice donor site with its 3' LTR" lacks essential elements required to obtain the virus claimed because it does not accurately reflect the fact that the splice donor from the 3' LTR is translocated to the 5' LTR. The

specification does not teach that reverse transcription as claimed ensures translocation of the splice donor.

III. Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-59 remain rejected and claims 60-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

Claim 1 as newly amended is indefinite. It appears that the vector of claim 1 is the vector obtained after reverse transcription and integration into the host cell genome because the splice donor has been translocated into the 5' LTR. The vector obtained after reverse transcription and integration into the host cell genome having the first NOI spliced as claimed does not have the first NOI as in item (d). In addition, the vector only has a portion of the 5' LTR and a portion of the splice donor spliced with a portion of the splice acceptor after splicing; it does not have the 5' LTR, functional splice acceptor or donor as claimed. Thus, the structure of the vector claimed is not clearly set forth.

Claim 6 is indefinite because "the expression product thereof" lacks antecedent basis. The NOI may be a packaging signal or regulatory element that is not expressed. It is unclear whether applicants are limiting the NOI to only those NOI that express proteins or if the NOI can be any nucleotide sequence of interest.

Claims 47 and 74 are indefinite because the step of "packaging the retroviral pro-vector in a packaging cell, thereby producing a viral particle" is unclear. It is unclear if the step of "packaging" refers to transfecting a packaging cell with the retroviral pro-

vector or to the production of a viral particle from a packaging cell transfected with the retroviral pro-vector.

Claims 47 and 74 are indefinite because the step of "infecting a target cell with the viral particle, wherein the retroviral pro-vector is reverse transcribed" does not result in producing a retroviral vector having a functional splice donor site with the 5' LTR as claimed. It is not clear that reverse transcription ensures translocation of the splice donor site to the 5' LTR.

The metes and bounds of a "heterologous transcriptional control sequence" in claims 55, 60-62 and 75-78 are unclear. Heterologous is a relative term; however, it cannot be determined to what the control sequence is "heterologous" in the claim, e.g. the NOI, the vector, the packaging cell or the target cell. As such, the metes and bounds of a "heterologous transcriptional control sequence" in the pro-vector cannot be determined.

Claim 57 as newly amended is indefinite. It appears that the vector of claim 57 is the vector obtained after reverse transcription and integration into the host cell genome because the splice donor has been translocated into the 5' LTR. The vector obtained after reverse transcription and integration into the host cell genome having the "intervening sequence between the functional splice donor and acceptor sites" spliced as claimed has only a portion of the 5' LTR after splicing and a portion of the splice donor spliced with a portion of the splice acceptor; it does not have the 5' LTR, functional splice acceptor or donor as claimed. Thus, the structure of the vector claimed is not clearly set forth.

Claim 57 is indefinite. The vector has an NOI (d), yet the vector has an "intervening sequence between the functional splice donor and the functional splice acceptor removed as a result of splicing (last lines of the claim). It is unclear if the vector claimed has the NOI or if the NOI has been removed as a result of splicing. It is unclear if the vector claimed has the intervening sequence or if the intervening sequence has been removed as a result of splicing. Thus, the structure of the vector claimed is unclear.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER